UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/327,761	06/07/1999	DONALD W. PETERSEN	99.501	5876

826 7590 06/07/2005

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
WITZ, JEAN C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/327,761	**Applicant(s)** PETERSEN ET AL.	
	Examiner Jean C. Witz	**Art Unit** 1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 March 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *11 March 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Jean C. Witz
Primary Examiner
Art Unit: 1651

S.o o

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed March 11, 2005 have been fully considered but they are not persuasive for the reasons set forth below.

Applicants assert that there is no motivation to combine the calcium sulfate hemihydrate of Yim with the composition of O'Leary. Applicant asserts that "it is clear that this reference [O'Leary] is directed to compositions that are intended to maintain a certain consistency for an extended period of time" and that "there is nothing in O'Leary to indicated that a composition that hardens or sets over time is envisioned." Applicants argue because the composition may be prepared in advance; it appears that Applicants are asserting that O'Leary teaches away from the claimed invention. These arguments are not persuasive for four reasons. First, in response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Second, Applicants' use of the term "extended" is subjective and not supported by the disclosure of O'Leary. Virtually all of the bone graft substitutes of the prior art require a workable consistency; however, that includes a broad variety of consistencies and the nature of the consistency is related to the individual circumstances of each defect. O'Leary at col. 3, lines 20-35, indicates that "consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like a putty, to those

which are runny." Further, the ultimate goal of these bone graft substitutes is the fact that the area where the substitutes are applied are ultimately hardened by the infiltration of the area of the defect with organic and inorganic bone tissue. Nowhere in O'Leary is the term "extended" used or defined. Third, Applicants appear to be suggesting that O'Leary must identify a problem in order to be used in a rejection based upon obviousness; however, there is no requirement in the patent law as to which specific piece of prior art provides the motivation to combine the references. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). So long as at least one of the prior art references provides the motivation, the requirements of the statute are met. Finally, O'Leary et al. disclose at col. 2, line 53 to col. 3, line 13, that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements. Calcium sulfate would be considered by one of ordinary skill in the art to be such an "inorganic element". Applicants' arguments that O'Leary teaches away from the claimed invention are based upon only a single embodiment. The composition may also be produced for immediate use.

Applicants assert that while "Yim purports to suggest composition including both calcium sulfate hemihydrate and certain cellulosic materials that are described as protein sequestering agents", "this combination does not appear in any examples . . . ." Applicants' assertion fails to address, for example, the statement found at col. 2, lines

27-31, found in the Summary of the Invention section, which identifies another embodiment of the invention of Yim, specifically "[y]et another embodiment of the present invention comprises formulation of osteogenic protein and a suitable quantity of a CSHS. The formulation may optionally include other protein sequestering agents, particularly cellulosic materials." Therefore, it is clear that Yim does suggest the combination of osteogenic proteins, CSHS and a cellulosic material (as defined at col. 7 and within the scope of the claimed "plasticizing substance") for repair of bone. One of ordinary skill in the art is well aware that compositions that contain osteogenic proteins include demineralized bone matrix (DBM) and that demineralized bone matrix is a common source of these proteins; in fact, this is one of the reasons why O'Leary uses DBM in his formulation, i.e. as a source of these proteins. See O'Leary at col. 1, lines 15-21.

Applicants continue to assert that the teaching of the Yim reference to include calcium sulfate hemihydrate in a bone graft formulation must be limited to the formulation of U.S. Patent 5,171,579, and therefore, there is no motivation to include it in the composition of O'Leary et al. Applicants also appear to be repeating an argument made previously that the inclusion of calcium sulfate of Yim into the composition of O'Leary is not necessary (and therefore not motivated) since "the O'Leary patent seems to suggest that the consistency of the 'flowable' material can be adjusted simply by altering the amount of the liquid component (column 3, lines 28-35). In the previous office action, Applicant asserted that the "reasons for adding calcium sulfate are either

inconsistent with the type of compositions that O'Leary intended to form or have already been addressed by O'Leary."

Yim specifically teaches that "[t]o reduce the preparation time and improve the above formulation's handling characteristics, [Patentees] have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate, also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS reduces setup time and provides improved moldability and consistency of the resulting formulation." Applicants appear to be asserting that Yim only suggests CSHS provides such advantages solely in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). This argument is not persuasive since Applicants do not address that the formulation discussed by Yim supra also includes a suitable "protein-sequestering agent", disclosed at col. 7, lines 25-34, as cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose. Yim already includes the thickener of O'Leary yet finds that the addition of calcium sulfate improves the composition for certain applications. As a result, one of ordinary skill in the art would expect the composition of O'Leary would similarly be improved for certain applications by the inclusion of calcium sulfate.

Further, in their argument that Yim does not discuss improvements in handling for the preferred embodiment described at col. 8, lines 16-28, Applicants also err in requiring that any prior art document must explicitly identify a problem to be solved in another specific formulation in order to provide motivation. Yim shows that bone repair compositions that do not contain CSHS will have improved moldability upon the inclusion of the CSHS and provides a reasonable expectation of success based upon the known properties of CSHS. This teaching is not negated simply because Yim does not identify all specific extant bone repair formulations that do not contain CSHS or discuss all aspects of improvements obtained by the combinations of ingredients. Again, such a requirement is not consistent with existing patent law and would, in fact, be onerous.

Applicants assert that there is no motivation to combine the teachings of Gertzman with O'Leary. Applicants focus on the difference between O'Leary and Gertzman but fail to address the similarities or the basis of motivation for combination set forth in the previous office actions. Applicants fail to address the importance of the Gertzman reference to the rejection as stated in Paper #15. The patent to Gertzman shows that malleable pastes are preferred in treating bone defects and that numerous substances are well known to be included in compositions for treating bone defects such as autologous bone, allograft bone, bone marrow and blood.

Applicants continue to argue that Gertzman teaches away from the composition of O'Leary by pointing out the discussions in Gertzman which address issues with a composition identified in Gertzman as GRAFTON® and is described as a "simple

mixture of glycerol and lyophilized, demineralized bone powder of a particle size in the range of 0.1 cm to 1.2 cm." Applicants assed that the teaching of Gertzman that GRAFTON® has been "runny" when placed in vivo, as well as discussions in Gertzman about the potential toxicity of glycerol is sufficient to teach away from the disclosure of O'Leary et al. However, review of col. 2, lines 40-55, shows that Gertzman states that GRAFTON®

> "works well to allow the surgeon to place the allograft bone material at the site. However, the carrier, glycerol has a very low molecular weight (92 Daltons) and is very soluble in water, the primiary component of the blood which flows at the surgical site.' Glycerol also experiences a marked reduction in viscosity when its temperature rises from room temperature (typically 22°C in an operating room) to the temperature of the patient's tissue, typically 37°C. This combination of high water solubility and reduced viscosity causes the allograft bone material to be "runny" and to flow away from the site almost immediately after placement', this prevents the proper retention of the bone within the site as carefully placed by the surgeon."

This "teaching away" appears to be limited to the use of glycerol, specifically since the quote above constantly refers to glycerol and not the other ingredients. Since the teaching of O'Leary is not limited to the GRAFTON® composition and therefore, Applicants' arguments are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (571) 272-0927. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jean C. Witz
Primary Examiner
Art Unit 1651